IN THE SPECIFICATION

Please amend the specification, as follows:

On page 1, lines 6-11, please amend the paragraph as follows:

--This application claims the benefit of US Provisional Patent Applications, Serial No. 60/410,541 ~~(CiDRA Docket No. CC-543)~~, filed Sept. 12, 2002, and is a continuation-in-part of US Patent Applications, Serial No. 10/645,686 (publication no. 2004/0075907 A1) ~~(CiDRA Docket No. CC-0649)~~, and a continuation-in-part of US Patent Applications, Serial No. 10/645,689 (publication no. ...) ~~(CiDRA Docket No. CC-0649)~~, each of which are incorporated herein by reference in their entirety. --

On page 1, lines 13-15, please amend the paragraph as follows:

--US Patent Application Serial No. 10/661,082 (publication no. US 2004 - 0179267 A1), filed concurrently herewith, entitled "Method and Apparatus for Labeling Using Diffraction Grating -Based Encoded Optical Identification Element" ~~(CiDRA Docket No. CC-0650A)~~, filed contemporaneously herewith, contains subject matter related to that disclosed herein, which is incorporated by reference in its entirety.--

On page 2, lines 3-5, please amend the paragraph as follows:

-- In a known DNA/genomic sequencing assay, each probe consists of known DNA sequences of a predetermined length, which are attached to a labeled (or encoded) bead ~~or~~ to a known location or spot on a substrate. --

On page 2, lines 6-15, please amend the paragraph as follows:

-- When the labeled target analyte is mixed with the probes, segments of the DNA sequence of the labeled target analyte will selectively bind to complementary segments of the DNA sequence of the known probe. The known probes are then spatially separated and examined for fluorescence. The probes ~~beads~~ that fluoresce indicate that the DNA sequence strands of the target analyte have attached or hybridized to the complementary DNA on that bead or spot. The DNA sequences in the target analyte can then be determined by knowing the complementary DNA (or cDNA) sequence of each known probe to which the labeled target is attached. In addition the level of fluorescence is indicative of how many of the target molecules hybridized to the probe molecules for a given probe ~~bead~~.--

On page 3, lines 22-28, please amend the paragraph as follows:

--According to the present invention, an optical identification element attached to a chemical, comprises: an optical substrate; at least a portion of said substrate having at least one diffraction grating disposed therein, said grating having at least one refractive index variation at a grating location, said grating being embedded within a substantially single material of said substrate ~~pitch superimposed at a common location~~; the grating providing an output optical signal when illuminated by an incident light signal propagating in free space, said code identifying at least one of the element and said chemical, said output signal not being the result of laser action with said grating when illuminated by said incident light signal; ~~said optical output signal being indicative of a code in said substrate;~~

and the chemical being attached to the at least a portion of said substrate.--

On page 3, lines 18-21, please amend the paragraph as follows:

--Objects of the present invention include ~~a diffraction grating based~~ encoded micro-particles that are coated with a substance for multiplexed experiments, which are very small, capable of providing a large number of unique codes, and/or ~~have~~ are resistant to harsh environments.--

On page 4, lines 12-13, please amend the paragraph as follows:

--The invention may be used in any assay or multiplexed experiment. The assay ~~stick 7~~ may be reused or disposed upon completion of the assay. --

On page 8, lines 23-26, please amend the paragraph as follows:

--The optical identification element 8 described herein is the same as that described in aforementioned Copending Patent Application Serial No. 10/661,234 ~~(CiDRA Docket No. CC-0648A)~~, filed contemporaneously herewith, which is incorporated herein by reference in its entirety.--

On page 11, lines 9-25, please amend the paragraph as follows:

--Referring to Figs. 3 - 8, the substrate 10 of the optical identification element (or microbead) 8 may be

functionalized by coating or attaching a desired probe 76, such as a compound, chemical or molecule, which is then used in an assay as an attractant for certain complimentary compounds, chemicals or molecules, otherwise known as a "target" analyte 52 – 54 (see Fig. 6). This capability to uniquely encode a large number of microbeads 8 with a corresponding unique probe 76 attached thereto enables these functionalized microbeads 72 to be mixed with unknown "target" analytes 52 - 54 to perform a multiplexed experiment. The procedure 40 for performing such a multiplexed assay or experiment includes the steps of producing (step 42) the microbead 8, as described hereinbefore, and functionalizing (step 44) the substrate 10 of the microbead 8 by coating/depositing/growing it with a probe 76 that will react in a predetermined way with "target" analytes 52 - 54. An assay is then performed (step 46) with a plurality of functionalized microbeads 72 with different identification codes 58 at the same time. In step 48, the fluorescence of the functionalized microbeads 72 is analyzed, and the functionalized microbead 72 is read to determine the code 58 thereof to thereby determine which "target" analytes ~~5~~ 52 – 54 are present in the solution 60.--

On pages 12-13, please amend the paragraph as follows:

--The "target" analytes 52 - 54 within the solution 60 are then mixed with the functionalized microbeads 72 - 74. During the mixing of the "target" analytes 52 - 54 and the functionalized microbeads 72 - 74, the "target" analytes attach to the complementary probes 76 – 78, as shown for

functionalized microbeads 72,73 having codes 12345678 and 34128913. Specifically, as shown in Fig. 6, "target" analytes 53 bonded with probes 76 of the functionalized microbeads 72 having the code 12345678, and "target" analytes 52 bonded with probes 77 of the functionalized microbeads 73 having the code 34128913. On the other hand, "target" analytes 54 did not bond with any probes, and no ~~not~~ "target" analytes 52 – 54 in the solution 60 bonded with probes 78 of the functionalized microbeads 74 having the code 11778154. Consequently, knowing which "target" analytes attach to which probes along with the capability of identifying each probe by the encoded microbead, the results of the assay would show that the unknown "target" analytes in the solution 60 includes "target" analytes 53, 54, as will be described in further detail.--

On pages 13-14, please amend the paragraph as follows:

--Once the reaction or combining is complete, the functionalized microbeads 72 - 74 are rinsed off with a saline solution to clean off the uncombined "target" analytes 52 - 54. As shown in Fig. 7, the functionalized microbeads 72 - 74 may be placed in a tray 84 with grooves 82 to allow the functionalized microbeads to be aligned in a predetermined direction, such as that described in U.S. Patent Application Serial No. 10/661,234 ~~(Cidra Docket No. CC-0648)~~, filed contemporaneously, which is incorporated herein by reference. The grooves 82 may have holes (not shown) that provide suction to keep the functionalized microbeads in position. Once aligned in the tray 84, the functionalized microbeads 52 - 54 are

individually scanned and analyzed by the bead detector 20.--

On page 14, lines 3-16, please amend the paragraph as follows:

--As best shown in Fig. 8, each functionalized microbead 72 - 74 is detected for fluorescence and analyzed to determine the identification code 58 of the functionalized microbeads. A light source (not shown) may be provided to luminate the microbeads 72 - 74. Once the fluorescent microbeads 72 - 74 are identified and knowing which probe 76 – 78 (or single strand of DNA) was attached to each coded, functionalized microbead 72 - 74, the bead detector 20 determines which "target" analytes 52 -54 were present in the solution 60. As described hereinbefore, the bead detector 20 illuminates the functionalized microbeads 72 - 74 and focuses light 26 reflected by the diffraction grating 12 through a lens 28 onto a CCD array or camera 32, whereby the code 58 of the functionalized microbead 72 - 74 is determined. Secondly, the bead detector 20 includes a fluorescence detector 86 for measuring the fluorescence emanating from "target" analytes 52 - 54 attached to the probes 76 - 78. The fluorescence meter 86 includes a lens 88 and optical fiber 90 for receiving and providing the fluorescence from the "target" analyte 52 - 54 to the fluorescence meter.--

On page 15, lines 1-10, please amend the paragraph as follows:

--For assays that use fluorescent molecule markers to label or tag chemicals, an optical excitation signal 800 is incident on the microbeads 8 through the tray 84 and a fluorescent optical output signal 802 emanates from the

beads 8 that have the fluorescent molecule attached. The fluorescent optical output signal 802 passes through a lens 804, which provides focused light 806 ~~802~~ to a known optical fluorescence detector 808. Instead of or in addition to the lens 804 ~~802~~, other imaging optics may be used to provide the desired characteristics of the optical image/signal onto the fluorescence detector 808. The detector 808 provides an output signal on a line 810 indicative of the amount of fluorescence on a given bead 8, which can then be interpreted to determine what type of chemical is attached to the bead 10.--

On page 15, lines 16-29, please amend the paragraph as follows:

--The code signal 822 from the bead code reader 820 and the fluorescent signal 810 from the fluorescence detector are provided to a known computer 812. The computer reads the code associated with each bead and determines the chemical probe that was attached thereto from a predetermined table that correlates a predetermined relationship between the bead code and the attached probes ~~probed~~. In addition, the computer 812 ~~and~~ reads the fluorescence associated with each bead and determines the sample or analyte that is attached to the bead from a predetermined table that correlates a predetermined relationship between the fluorescence tag and the analyte attached thereto. The computer 812 then determines information about the analyte and/or the probe as well as about the bonding of the analyte to the probe, and provides such information on a display, printout, storage medium or other interface to an operator, scientist or database for review and/or analysis. The sources 801, 803 the code

reader 820, the fluorescence optics 804 and detector 808 and the computer 812 may all be part of an assay ~~stick~~ reader 824.--

On page 16, lines 7-24, please amend the paragraph as follows:

--Generally, the assay of the present invention may be used to carry out any binding assay or screen involving immobilization of one of the binding agents. Such solid-phase assays or screens are well known in the chemical and biochemical arts. For example, such screening may involve specific binding of cells to a molecule (e.g. an antibody or antigen) immobilized on a microbead in the assay ~~stick~~ followed by analysis to detect whether or to what extent binding occurs. Alternatively, the beads may be subsequently removed from the assay ~~stick~~ for sorting and analysis via flow cytometry (see e.g. by Needels et al. (1993). Examples of biological compounds that may be assayed or screened using the assay ~~stick~~ of the present invention include, e.g. agonists and antagonists for cell membrane receptors, toxins, venoms, viral epitopes, hormones, sugars, cofactors, peptides, enzyme substrates, drugs inclusive of opiates and steroids, proteins including antibodies, monoclonal antibodies, antisera reactive with specific antigenic determinants, nucleic acids, lectins, polysaccharides, cellular membranes and organelles. In addition, the present invention may be used in any of a large number of well-known hybridization assays where nucleic acids are immobilized on a surface of a substrate, e.g. genotyping, polymorphism detection, gene expression analysis, fingerprinting, and other methods of DNA- or RNA-based sample analysis or diagnosis.--

On pages 16-17, please amend the paragraph as follows:

--Any of the great number of isotopic and non-isotopic labeling and detection methods well-known in the chemical and biochemical assay art may be used to detect binding with the present invention. Alternatively, spectroscopic methods well-known in the art may be used to determine directly whether a molecule is bound to a surface coating in a desired configuration. Spectroscopic methods include e.g., UV-VIS, NMR,EPR, IR, Raman, mass spectrometry and other methods well-known in the art. For example, mass spectrometry also is now widely employed for the analysis of biological macromolecules. The method typically involves immobilization of a protein on a surface of substrate where it is then exposed to a ligand binding interaction. Following ligand binding (or non-binding) the molecule is desorbed from the surface and into a spectrometer using a laser (see, e.g. Merchant and Weinberger, "Recent advancements in surface-enhanced laser desorption/ionization-time of flight-mass spectrometry," Electrophoresis 21: 1164-1177 (2000)). The microbeads in the assay ~~stick~~ of the present invention may be used as substrates in the mass spectrometry detection methods described above.--.

On pages 17-18, please amend the paragraph as follows:

--Some current techniques used in combinatorial chemistry or biochemistry are described in US Patent No. 6,294,327, entitled "Apparatus and Method for Detecting Samples Labeled With Material Having Strong Light Scattering Properties, Using Reflection Mode Light and

Diffuse Scattering", issued Sept. 23, 2001 to Walton et al.; US Patent No. 6,242,180, entitled "Computer Aided Visualization and Analysis System for Sequence Evaluation", issued June 5, 2001, to Chee; US Patent No. 6,309,823 entitled "Arrays of Nucleic Acid Probes for Analyzing Biotransformation of Genes and Methods of Using the Same", Oct. 30, 2001, to Cronin et al.; US Patent No. 6,440,667, entitled "Analysis of Target Molecules Using an Encoding System"; US Patent No. 6,355,432, entitled "Products for Detecting Nucleic Acids"; US Patent No. 6,197,506, entitled "Method of Detecting Nucleic Acids"; US Pat No. 6,309,822, entitled "Method for comparing copy number of nucleic acid sequences"; US Patent No. 5,547,839, entitled "Sequencing of surface immobilized polymers utilizing micro- fluorescence detection", US Patent No. 6,383,754, entitled "Binary Encoded Sequence Tags", and US Patent Nos. 6,261,782 and 6,667,121 ~~No. 6,383,754~~, entitled "Fixed Address Analysis of Sequence Tags", which are all incorporated herein by reference to the extent needed to understand the present invention.--

On page 19, lines 9-17, please amend the paragraph as follows:

--Referring to Fig. 10, the ~~The~~ reflected light 27, comprises a plurality of beams 26-36 that pass through a lens 37, which provides focused light beams 46-56, respectively, which are imaged onto a CCD camera 60. The lens 37 and the camera 60, and any other necessary electronics or optics for performing the functions described herein, make up the reader 29. Instead of or in addition to the lens 37, other imaging optics may be used to provide

the desired characteristics of the optical image/signal onto the camera 60 (e.g., spots, lines, circles, ovals, etc.), depending on the shape of the substrate 10 and input optical signals. Also, instead of a CCD camera other devices may be used to read/capture the output light.--

On page 22, lines 23-27, please amend the paragraph as follows:

Referring to Fig.13, illustrations (a)-(c), for the grating 12 in a cylindrical substrate 10 having a sample spectral 17 bit code (i.e., 17 different pitches Λ1-Λ17), the corresponding image on the CCD (Charge Coupled Device) camera 60 is shown for a digital pattern of 17 bit locations 89, including Figure 13, illustrations (b), (c) and (d), respectively, for 7 bits turned on (10110010001001001); 9 bits turned on of (11000101010100111); and all 17 bits turned on of (11111111111111111).--

On page 25, lines 13-26, please amend the paragraph as follows:

--In Fig. 15, the bits may be detected by continuously scanning the input wavelength. A known optical source 300 provides the input light signal 24 of a coherent scanned wavelength input light shown as a graph 304. The source 300 provides a sync signal on a line 306 to a known reader 308. The sync signal may be a timed pulse or a voltage ramped signal, which is indicative of the wavelength being provided as the input light 24 to the substrate 10 at any given time. The reader 308 may be a photodiode, CCD camera, or other optical detection device that detects when an optical signal is present and provides an output signal on a line 309 indicative of the code in the substrate 10 or of the wavelengths present in the output

light, which is directly related to the code, as discussed herein. The grating 12 reflects the input light 24 and provides an output light signal 310 to the reader 308. The wavelength of the input signal is set such that the reflected output light 310 through an optical lens 321 will be substantially in the center 314 of the Bragg envelope 200 for the individual grating pitch (or bit) being read.--

On pages 25-26, please amend the paragraph as follows:

--Alternatively, the source 300 may provide a continuous broadband wavelength input signal such as that shown as a graph 316. In that case, the reflected output beam 310 signal is provided to a narrow band scanning filter 318 which scans across the desired range of wavelengths and provides a filtered output optical signal 320 through an optical reader 321 to the reader 308. The filter 318 provides a sync signal on a line 322 to the reader, which is indicative of which wavelengths are being provided on the output signal 320 to the reader and may be similar to the sync signal discussed hereinbefore on the line 306 from the source 300. In this case, the source 300 does not need to provide a sync signal because the input optical signal 24 is continuous. Alternatively, instead of having the scanning filter being located in the path of the output beam 310, the scanning filter may be located in the path of the input beam 24 as indicated by the dashed box 324, which provides the sync signal on a line 323.--

On page 27, lines 11-16, please amend the paragraph as follows:

--In this case, rather than having the input light 24 coming in at the conventional Bragg input angle θi, as discussed hereinbefore and indicated by a dashed line 701, the grating 12 is illuminated with the input light 24 oriented on a line 705 orthogonal to the longitudinal grating vector

703 ~~705~~. The input beam 24 will split into two (or more) beams of equal amplitude, where the exit angle θ_o can be determined from Eq. 1 with the input angle θ_i=0 (normal to the longitudinal axis of the grating 12). --

On page 27, lines 17-23, please amend the paragraph as follows:

--In particular, from Eq. 1, for a given grating pitch Λ1, the +/-1st order beams (m=+1 and m=-1), corresponds to output beams 700,702, respectively. For the +/-2nd order beams (m=+2 and m=-2), corresponds to output beams 704,706, respectively. The 0th order (undiffracted) ~~(undefracted)~~ beam (m=0), corresponds to beam 708 and passes straight through the substrate. The output beams 700-708 project spectral spots or peaks 710-718, respectively, along a common plane, shown from the side by a line 709, which is parallel to the upper surface of the substrate 10. --

On page 30, lines 12-25, please amend the paragraph as follows:

--Referring to Fig. 21, instead of using an optical binary (0-1) code, an additional level of multiplexing may be provided by having the optical code use other numerical bases, if intensity levels of each bit are used to indicate code information. This could be achieved by having a corresponding magnitude (or strength) of the refractive index change (δn) for each grating pitch Λ. Four intensity ranges are shown for each bit number or pitch Λ, providing for a Base-4 code (where each bit corresponds to 0,1,2, or 3). The lowest intensity level, corresponding to a 0, would exist when this pitch Λ is not present in the grating 12. The next intensity level 450 would occur when a first low level

δn1 exists in the grating that provides an output signal within the intensity range corresponding to a 1. The next intensity level 452 would occur when a second higher level δn2 exists in the grating 12 that provides an output signal within the intensity range corresponding to a 2. The next intensity level 454 ~~452~~, would occur when a third higher level δn3 exists in the grating 12 that provides an output signal within the intensity range corresponding to a 3.--

On page 32, lines 12-25, please amend the paragraph as follows:

--Referring to Fig. 23, if the value of n1 in the grating region 20 is greater than the value of n2 in the non-grating region 18, the grating region 20 of the substrate 10 will act as a known optical waveguide for certain wavelengths. In that case, the grating region 20 acts as a "core" along which light is guided and the outer region 18 acts as a "cladding" which helps confine or guide the light. Also, such a waveguide will have a known "numerical aperture" (θna) that will allow light 630 that is within the aperture θna to be directed or guided along the grating axis 207 and reflected axially off the grating 12 and returned and guided along the waveguide. In that case, the grating 12 will reflect light having the appropriate wavelengths equal to the pitches Λ present in the grating 12 back along the region 20 (or core) of the waveguide, and pass the remaining wavelengths of light as the light 632. Thus, having the grating region 20 act as an optical waveguide for wavelengths reflected by the grating 12 allows incident light that is not aligned exactly with the grating axis 207 to be guided along and aligned with the grating 12 axis 207 for optimal grating reflection.--

On pages 37-38, please amend the paragraph as follows:

--Referring to Fig. 33, illustrations (a), (b), (c), (d), and (e) the substrate 10 may have one or more holes located within the substrate 10. In illustration (a), holes 560 may be located at various points along all or a portion of the length of the substrate 10. The holes need not pass all the way through the substrate 10. Any number, size and spacing for the holes 560 may be used if desired. In illustration (b), holes 572 may be located very close together to form a honeycomb-like area of all or a portion of the cross-section. In illustration (c), one (or more) inner hole 566 may be located in the center of the substrate 10 or anywhere inside of where the grating region(s) 20 are located. The inner hole 566 may be coated with a reflective coating 573 to reflect light to facilitate reading of one or more of the gratings 12 and/or to reflect light diffracted off one or more of the gratings 12. The incident light 24 may reflect off the grating 12 in the region 20 and then reflect off the surface 573 to provide output light 577. Alternatively, the incident light 24 may reflect off the surface 573, then reflect off the grating 12 and provide the output light 575. In that case the grating region 20 may run axially or circumferentially 571 around the substrate 10. In illustration (d), the holes 579 may be located circumferentially around the grating region 20 or transversely across the substrate 10. In illustration (e), the grating 12 may be located circumferentially around the outside of the substrate 10, and there may be holes 574 inside the substrate 10. <u>In that case, the incident light 24 reflects off the grating 12 to provide the optical light 576.</u>--

On page 38, lines 20-22, please amend the paragraph as follows:

--Referring to Fig. 36, at least a portion of a side of the substrate 10 may be coated with a reflective coating 514 to allow incident light 510 to be reflected back to the same side from which the incident light came, as indicated by reflected light 512.--

On pages 39-40, please amend the paragraph as follows:

--Referring to Fig. 37, illustrations (a) and (b), alternatively, the substrate 10 can be electrically and/or magnetically polarized, by a dopant or coating, which may be used to ease handling and/or alignment or orientation of the substrate 10 and/or the grating 12, or used for other purposes. Alternatively, the bead may be coated with conductive material, e.g., metal coating on the inside of a ~~holy~~ holey substrate, or metallic dopant inside the substrate. In these cases, such materials can cause the substrate 10 to align in an electric or magnetic field. Alternatively, the substrate can be doped with an element or compound that fluoresces or glows under appropriate illumination, e.g., a rare earth dopant, such as Erbium, or other rare earth dopant or fluorescent or luminescent molecule. In that case, such fluorescence or luminescence may aid in locating and/or aligning substrates.--